nAChRs mediate human embryonic stem cell-derived endothelial cells: proliferation, apoptosis, and angiogenesis.

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Public Summary:
BACKGROUND: Many patients with ischemic heart disease have cardiovascular risk factors such as cigarette smoking. We tested the effect of nicotine (a key component of cigarette smoking) on the therapeutic effects of human embryonic stem cell-derived endothelial cells (hESC-ECs). METHODS AND RESULTS: To induce endothelial cell differentiation, undifferentiated hESCs (H9 line) underwent 4-day floating EB formation and 8-day outgrowth differentiation in EGM-2 media. After 12 days, CD31(+) cells (13.7+/-2.5%) were sorted by FACScan and maintained in EGM-2 media for further differentiation. After isolation, these hESC-ECs expressed endothelial specific markers such as vWF (96.3+/-1.4%), CD31 (97.2+/-2.5%), and VE-cadherin (93.7+/-2.8%), form vascular-like channels, and incorporated DiI-labeled acetylated low-density lipoprotein (DiI-Ac-LDL). Afterward, 5x10(6) hESC-ECs treated for 24 hours with nicotine (10(-8) M) or PBS (as control) were injected into the hearts of mice undergoing LAD ligation followed by administration for two weeks of vehicle or nicotine (100 microg/ml) in the drinking water. Surprisingly, bioluminescence imaging (BLI) showed significant improvement in the survival of transplanted hESC-ECs in the nicotine treated group at 6 weeks. Postmortem analysis confirmed increased presence of small capillaries in the infarcted zones. Finally, in vitro mechanistic analysis suggests activation of the MAPK and Akt pathways following activation of nicotinic acetylcholine receptors (nAChRs). CONCLUSIONS: This study shows for the first time that short-term systemic administrations of low dose nicotine can improve the survival of transplanted hESC-ECs, and enhance their angiogenic effects in vivo. Furthermore, activation of nAChRs has anti-apoptotic, angiogenic, and proliferative effects through MAPK and Akt signaling pathways.

Scientific Abstract:
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